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Properly tuned first fluoride-catalyzed TGME-mediated amination process for chloroimidazoles: inexpensive technology for antihistaminic norastemizole

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Abstract

Fluoride-catalyzed amination process of chloroimidazole **1** proved to be a practical and inexpensive procedure for the preparation of the antihistaminic, norastemizole.

Imidazole containing heterocyclic compounds have been studied extensively due to their varied biological activity toward numerous diseases.[1] Aminoimidazole derivatives represent a chemically and pharmacologically important subclass of this heterocyclic family.[2] During the development of a potent antihistamine, norastemizole,[3] we required an economical large-scale process for the assembly of the aminoimidazole framework. There has been an enormous amount of work published in the area of fluoride activation of the carbon nucleus and conversion of the C–F bond to the C–N bond.[4] Surprisingly, in the imidazole chemistry only a few reports have been disclosed.[5] However, existing processes for the synthesis of sensitive 2-F-imidazoles are impractical[6] and require isolation and purification prior to the reaction with amine. Therefore, the development of a direct conversion of readily available 2-Cl imidazoles to aminoimidazole utilizing an appropriately defined 'Fluoride-Vehicle' would be an extremely valuable addition to imidazole chemistry. In addition, we envisaged that development of a fluoride-catalyzed amination process of a less activated C–Cl bond of imidazole to the C–N bond via polarized C–F bond will have a special niche over existing Pd-mediated amine coupling process of 2-chloro imidazoles[3b,c] because most of the fluoride sources are inexpensive, readily available, environmentally friendly and more suited to large-scale pharmaceutical processes such as norastemizole synthesis. We now report a new and practical solution for the conversion of chloroimidazoles to aminoimidazoles via first fluoride-catalyzed TGME-assisted amination process.

First we investigated the preparation of 4-fluorobenzyl-2-fluorobenzimidazole. Initial attempts to generate 4-fluorobenzyl-2-fluorobenzimidazole from 4-fluorobenzyl-2-chlorobenzimidazole with TBAF

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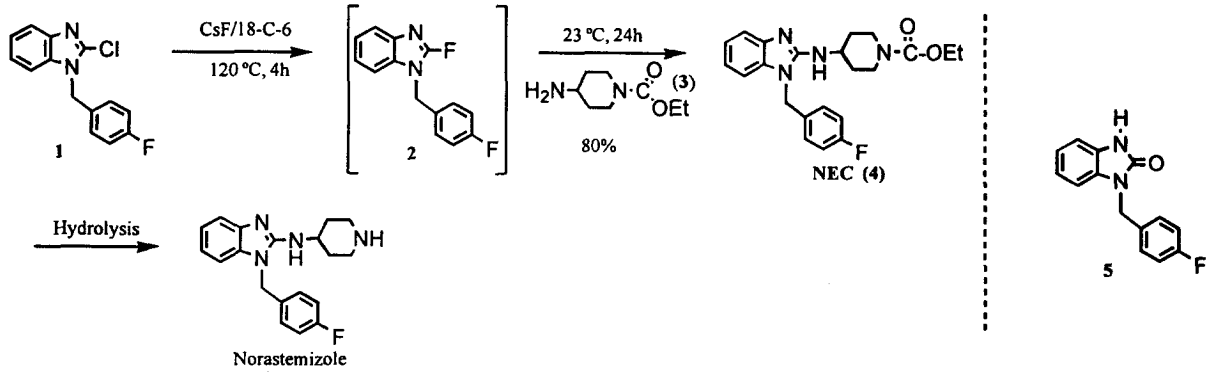
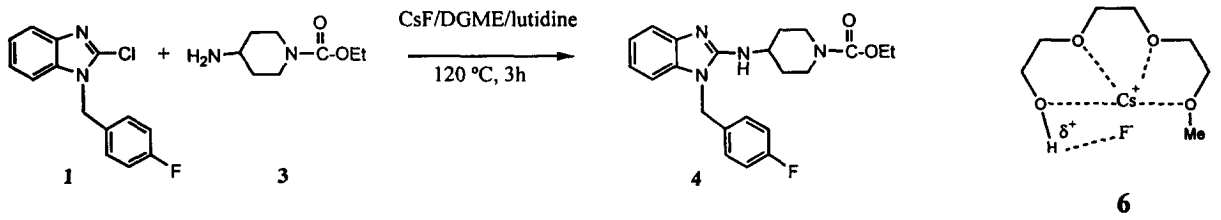
or cyanuric fluoride in dioxane at reflux afforded low conversion by HPLC analysis. Interestingly, substitution of TBAF with excess KF in 18-C-6 as a solvent at 120°C provided only 50% conversion to the fluoro intermediate **2** after 24 h. However, heating with CsF (4 equiv.) in 18-C-6 at 120°C for 4 h provided 4-fluorobenzyl-2-fluorobenzimidazole in quantitative conversion by HPLC analysis. The mixture was then cooled to room temperature and treated with aminopiperidine **3** to provide quantitative conversion to the desired norastemizole ethyl carbamate (NEC, **4**) (24 h), which was isolated in 80% yield (Scheme 1). If the reaction was conducted at 120°C, the coupling was complete within <2 h.[7] A control experiment indicated that without CsF, the coupling process proceeded extremely slowly (>60 h) and high levels of urea **5** were found. The CsF-mediated mild amination process was extremely fascinating. However, in order to develop a practical and cost effective amination process the following criteria had to be met: (1) 18-C-6 needed to be eliminated or substituted; and (2) the CsF source needed to be catalytic or replaced with an inexpensive and environmentally friendly fluoride source.



Scheme 1.

A variety of fluoride sources were initially examined in the coupling reaction between chloroimidazole **1** with 2 equiv. of amine **3** at 120°C. In all cases studied, stoichiometric amounts of fluoride sources such as, TBAF, TBAF·$4H_2O$, CsF, KF, or KFH_2 were used to screen their effect on the rate of the coupling process. The initial results indicated that the rate enhancement was observed in certain solvents by addition of fluoride salts such as TBAF or CsF. Interestingly, using NMP, DMAC, TMU, or DMF as the solvent, organic fluorides (TBAF, etc.) displayed a high degree of rate enhancement. However, inorganic fluorides (CsF, KF) provided no significant rate enhancement. On the other hand, inorganic fluorides such as, CsF, KF, $CaCO_3$-KF, and KFH_2 led to an increase in the reaction rate when solvents such as butanol, polyethers, or monoalkylpolyglyme were used. In addition, in all cases substantial quantities of urea **5** formation were observed. The urea formation process is mainly dependent on the pH of the media. When the reaction was conducted at either low pH (1–5) or high pH (>10) the formation of substantial quantities of urea **5** was observed. It was found that addition of 1 equiv. of either tertiary amine bases such as R_3N (Bu_3N, iPr_2EtN, etc.), or substituted pyridine-type bases[8] to the reaction mixture, minimized urea formation. The base effect or pH moderation in the course of the reaction was closely monitored. After considerable experimentation, either 2,6-lutidine or 2,4,6-collidine provided minimal urea **5** formation and was established to be the base of choice for the F^--mediated amination chemistry.[9] After defining the base (2,6-lutidine), systematic optimization of the F^- source and solvent was conducted. It is gratifying to disclose that the CsF-monomethyldiglyme (DGME) combination provided the highest rate enhancement with minimal by-product formation. The reaction is conducted as follows: The chloroimidazole **1** is dissolved in DGME and lutidine (1.10 equiv.), CsF (1.0 equiv.) are added, followed by amine **3** (1.05

equiv.) at 22°C. The mixture is then heated to 120°C for 3 h, to provide an isolated yield of >85% with a purity of >99% by HPLC analysis (Scheme 2).



Scheme 2.

After finding the proper reagent combination, the curious polyetheral solvent effect was re-examined. As depicted in Fig. 1, the monomethyl polyglyme type of solvents displayed the highest rate enhancement. It is important to note that the cyclic polyglyme solvents (for example: 18-C-6) or dimethylpolyglyme displayed a lower rate in the fluoride-mediated amination process. It is postulated that the monomethylpolyglymes play a critical role by acting as an organic soluble fluoride carrier by hydrogen bonding to the naked fluoride ion (see structure **6**). The increasing order of the rate of the reaction with the polyglyme type of solvents is as follows: TGME»DGEE>DGME>18-C-6>MGME>TGDE (Fig. 1).[10]

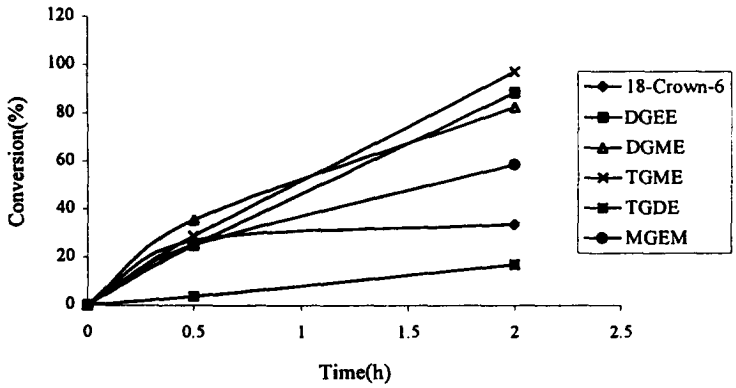


Figure 1. The solvent effects on the amine **3** coupling process

Next, we determined the influence of the alkali-metal cation on the rate of reaction and observed that the rate increased dramatically upon increasing the ionic radii (Cs>Rb>K>Na>Li, Fig. 2). Due to the high cost of CsF and RbF, KF was examined. It was found that 1 equiv. of spray dried-KF can substitute

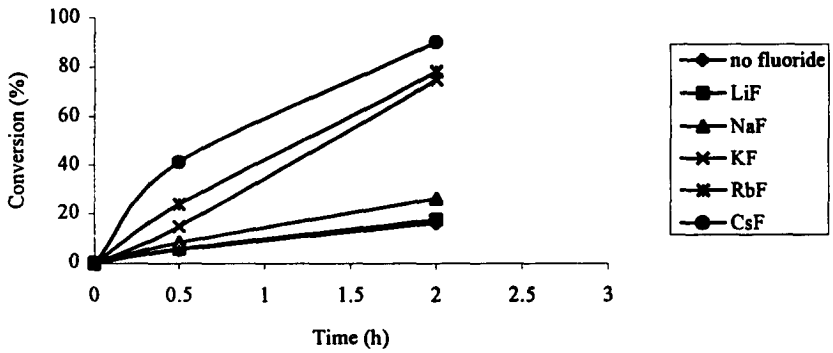
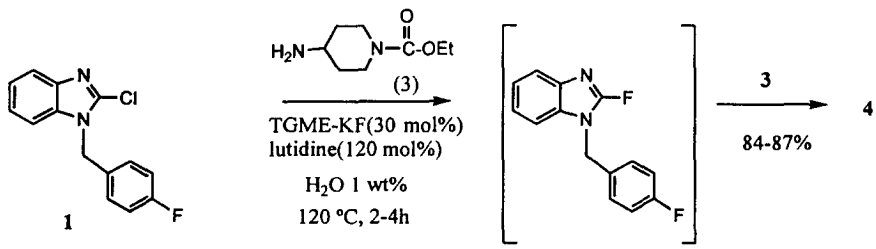


Figure 2. The effects of the MF on the amine **3** coupling process

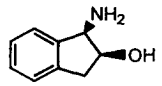
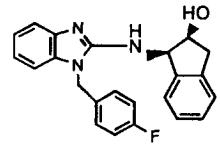
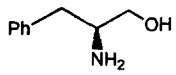
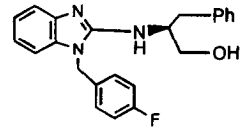
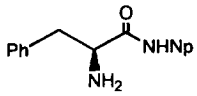
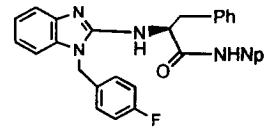
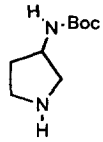
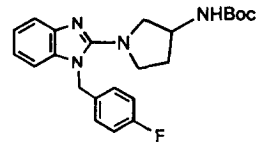
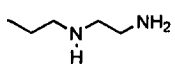
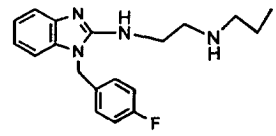
for CsF with only minimal lowering of the rate effect (Cs^+, 2 h versus K^+, 3 h). The KF acts as a catalyst: decreasing the mol% of KF from 100 to 30 gave a quantitative conversion to **4**, also without a drastic effect on the rate (100 mol%, 3 h versus 30 mol%, 5 h). With the expectation that water would alter the rate of the reaction, we introduced water to the reaction mixture.[11] We were pleased to discover that the addition of 1 wt% of water increased the rate about twofold. The maximum water tolerance of the reaction is up to 3 wt%. The optimal fluoride catalyzed amination process for compound **4** is shown in Scheme 3. This catalytic process is extremely *reproducible* and *robust. The viability of the fluoride catalyzed amination process was demonstrated on a multi-kilogram scale to produce >200 kg of compound 4 with an 87% isolated yield (99% purity, reaction time <2 h).*



Scheme 3. Optimal fluoride catalyzed amination process for norastemizole ethyl carbamate (**4**)

Due to the success and simplicity of the synthesis of the antihistamine norastemizole ethyl carbamate (**4**), the generality of the method was investigated (Table 1). In all cases, the conversion of the chloroimidazole **1** to aminoimidazole was >98% with good isolated yields (73–87%). Both amino alcohols and

Table 1

Entry	Amine	Solvent/MF/Base	Rn time	Product	yield %
1		TGME/ KF/lutidine	6h		76
2		TGME/ KF/lutidine 18-C-6/CsF	6h 2h		73 77
3		TGME/KF/lutidine	8h		87
4		TGME/KF/lutidine	3h		77
5		TGME/ KF/lutidine 18-C-6/CsF	3.5h 3.5h		82 80

amino acid derivatives coupled smoothly using this newly developed procedure (entries 1–3). In contrast, coupling *cis*-aminoindanol with chloroimidazole **1** using Pd-catalyzed process was unsuccessful.[12] As shown in entry 4, secondary amines coupled extremely well. In addition, selective amination of linear diamines are possible, and primary amines can be preferentially coupled in the presence of secondary amines (entry 5).

In conclusion, we have developed a novel and highly practical process for entry into medicinally important aminoimidazole derivatives via a fluoride catalyzed process. As far as we are aware, this represents the first example of a fluoride catalyzed amination process. The scope and limitations of this reaction are being explored further.

References

1. (a) Senanayake, C. H.; Fredenburgh, L. E.; Reamer, A. R.; Liu, J.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1994**, *35*, 5775, and references cited therein. (b) Janssens, F.; Torremans, J.; Janssen, M.; Stokbroekx, R. A.; Luyckx, M.; Janssen, P. A. *J. Med. Chem.* **1985**, *28*, 1925. (c) Jung, F.; Boucherot, D.; Delvare, C.; Olivier, A. *J. Antibiot.* **1993**, *46*, 993. (d) Fujimoto, K. *J. Antibiot.* **1987**, *40*, 370. (e) Simonov, A. M.; Arismovs, V. A. *Chem. Heterocycl. Compd.* **1979**, *15*, 705.
2. (a) Janssens, F.; Torremans, J.; Janssen, M.; Stokbroekx, R. A.; Luyckx, M.; Janssen, P. A. *J. Med. Chem.* **1985**, *28*, 1943. (b) Kym, O.; Ratner, L. *Ber.* **1912**, *45*, 3238. (c) Efros, L. S.; Porai, B. A. *Farbenshtein, Zhur. Obshch. Khim.* **1953**, *23*, 1691. (d) Brown, D. J. *J. Chem. Soc.* **1958**, 1974. (e) Grimmett, R. M. *Adv. Heterocycl. Chem.* **1970**, *12*, 103. (f) Grimmett, R. M. *Adv. Heterocycl. Chem.* **1980**, *27*, 241. (g) Subrayan, P. R.; Kampf, W. J.; Rasmussen, P. G. *J. Org. Chem.* **1994**, *59*, 4341.
3. (a) Hong, Y.; Tanoury, G. T.; Wilkinson, H. S.; Bakale, R. P.; Wald, S. A.; Senanayake, C. H. *Tetrahedron Lett.* **1997**, *38*, 5607. (b) Hong, Y.; Senanayake, C. H.; Xiang, T.; Vandenbossche, C. P.; Tanoury, G. J.; Bakale, R. P.; Wald, S. A. *Tetrahedron Lett.* **1998**, *39*, 3121. (c) Handley, D. A.; Hong, Y.; Bakale, R.; Senanayake, C. H. *Drugs of the Future* **1998**, *23(9)*, 966, and references cited therein.
4. Chambers, R. D. *Fluorine in Organic Chemistry*; A Wiley–Interscience publication, Antony Rowe Ltd., 1973; Chapter 9.
5. (a) McCleland, R. A.; Fuller, R. J.; Seaman, N. E. *Biochem. Pharmacol.* **1984**, *33*, 303. (b) Jung, F.; Boucherot, C.; Delvare, C.; Olivier, A. *J. Antibiotics* **1993**, 992. (c) Coad, C. E.; Kampf, J.; Rasmussen, P. G. *J. Org. Chem.* **1996**, *61*, 6666, and references cited therein.
6. (a) Takeuchi, Y.; Kirk, K. L.; Cohen, L. A. *J. Org. Chem.* **1978**, *43*, 3570. (b) Takahashi, K.; Kirk, K. L.; Cohen, L. A. *J. Org. Chem.* **1984**, *49*, 1951. (c) Bryce, M. R.; Chambers, S. T.; Mullins, S. T.; Parkin, A. *Bulletin De La Societe Chimique De Fr.* **1986**, *6*, 930. (d) Sono, M.; Toyoda, N.; Shizuri, Y.; Motoo, T. *Tetrahedron Lett.* **1994**, *35*, 9237. (e) Barrio, J. R.; Namavari, M.; Phelps, M. E.; Satyamurthy, N. *J. Am. Chem. Soc.* **1996**, *118*, 10408.
7. It is important to note that chloroimidazole couples with amine in the presence of the CsF-18-C-6 combination at lower temperatures; for example, at 80°C no coupling product formation was observed. At 100°C, the reaction proceeded slowly.
8. Utilizing pyridine as the base for this coupling reaction was unsuccessful.
9. When the base was lutidine, the pH of the reaction mixture was monitored and proved to be 8.5–9 in the course of the coupling process.
10. DGME=diglyme methyl ether; TGME=triglyme methyl ether; MGEM=monoglyme methyl ether; TGDM=triglyme dimethyl ether; DGEE=diglyme monoethyl ether; TGDE=triglyme dimethyl ether.
11. The reaction mixture is heterogeneous, therefore, addition of water increases the solubility of the catalyst system.
12. The Pd-catalyzed amination was pursued using the Buchwald–Hartwig type procedure described in Ref. 3b but was unsuccessful.